TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Letter to the Editor

Turk J Med Sci
(2021) 51: 2786-2788

doi:10.3906/sag-2102-84

Pretreatment serum uric acid level is not a surrogate marker for the outcome of favipiravir treatment in COVID-19 patients

Ahmet Çağkan İNKAYA[1,*], Emre KARA[2], Nursel ÇALIK BAŞARAN[3], Taha Koray ŞAHİN[3], Oğuz Abdullah UYAROĞLU[1], Ömrüm UZUN[1], Serhat ÜNAL[1]

[1]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Hacettepe University, Ankara, Turkey
[2]Department of Clinical Pharmacy, Faculty of Pharmacy, Hacettepe University, Ankara, Turkey
3Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey

Received: 06.02.2021 • **Accepted/Published Online:** 15.08.2021 • **Final Version:** 21.10.2021

To the editor,

Favipiravir (FVP) was developed against the influenza virus infection and licensed for the treatment of influenza in Japan [1]. In addition to influenza viruses, FVP demonstrates a broad-spectrum activity against many RNA viruses including Ebola, Lassa, rabies, and severe fever with thrombocytopenia [2]. FVP exhibited a comparable in vitro efficacy against SARS-CoV-2 with remdesivir in a cell culture model [3].

FVP is a prodrug and is metabolized to FVP-ribofuranosyl-5'-triphosphate (FVP-RTP) as the active form in cells by human hypoxanthine-guanine phosphoribosyltransferase (HGPRT) [1]. Besides, HGPRT is a critical enzyme in the purine salvage pathway that converts hypoxanthine to inosine monophosphate and guanine to guanosine monophosphate [4]. It is very well known that dysfunctions in the purine salvage pathway (i.e. low HGPRT activity) manifest with elevated uric acid levels. In this study, it was hypothesized that the patients with high serum uric acid levels may have lower HGPRT activity hindering the conversion of FVP to its active metabolite, which might, in turn, lead to a delayed response to FVP treatment in COVID-19 patients.

Patients over 18 years, admitted for COVID-19 between March 23 and June 23, 2020, were recruited in this cross-sectional study. Institutional review board approval was granted from the Hacettepe University Ethical Committee for Non-interventional Studies (GO 20/354). The patients were closely followed up, and routine blood tests were repeated on days 3 and 5 of their admission. Favipiravir was administered 1600 mg BID as an oral loading dose followed by 600 mg BID for 4 days. Standard of care treatments was given to all patients. Endpoints were defined as time-to-defervescence (body temperature <38°C), time-to-hospital discharge, and death. Serum uric acid levels were recorded at hospital admission, and all analyses were based on these results. People with underlying conditions (i.e. gout, chronic renal failure) and on medications (i.e. diuretics, allopurinol) that may affect serum uric acid levels were excluded. Because baseline serum uric acid levels were compatible with normal distribution, a cut-off point of 5 mg/dL (median value of the recruited cohort) was constituted to categorize the cohort into low and high uric acid groups.

Data of 80 confirmed patients were analyzed in this study. The mean age of the patients was 54.5 ± 16.9 years, and 47.5% (n = 39) of the patients were women. Disease severity was comparable between low and high uric acid groups ($p = 0.104$). Low and high uric acid groups were comparable in terms of comorbidities ($p > 0.05$). The mean baseline uric acid level was 5.1 ± 1.9 mg/dL. The patients were divided into two groups as those with uric acid level <5 mg/dL (low) (48.8%, n = 39) and ≥5 mg/dL (high) (51.3%, n = 41). The mean level of baseline lymphocyte, neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), ferritin, D-dimer, fibrinogen, ALT, AST, ALP, GGT, LDH were not statistically different between high and low uric acid groups. Only BUN and creatinine were higher in the high uric acid group ($p < 0.001$ and $p < 0.001$, respectively). Time to hospital discharge (THD) was 8.5 (1–45) and 9.5 (2–67) days in low uric acid and high uric acid groups, respectively ($p = 0.389$) (Table). The fatality rate was 12.2% (5/41) and 2.6% (1/39) in the high uric acid group and the low uric acid, respectively ($p = 0.102$). The median baseline uric acid level of those who died was 5.79 (4.90–7.60) mg/dL, and 4.94 (1.95–10.40) mg/dL in recovered patients ($p = 0.168$). Time to defervescence (TTD) was achieved in 5.00 ± 5.35 days

* Correspondence: inkayaac@yahoo.com

Table. Comparison of the changes in laboratory findings on the 3rd and 5th days between groups.

	Low uric acid group, median (minimum, maximum)		High uric acid group, median (minimum, maximum)		p-value*
Change from baseline on the 3rd day of FVP					
Lymphocyte (10^6/L)	395	(–2040, 780)	95	(–420, 900)	0.975
NLR	–1.08	(–8.14, 14.96)	–0.25	(–10.72, 34.33)	0.176
CRP (mg/dL)	–0.28	(–9.90, 10.73)	2.73	(–8.30, 21.60)	**0.011**
LDH (U/L)	–32	(–302, 204)	21	(–372, 333)	0.282
Ferritin (µg/L)	24.5	(–449, 695)	13.2	(–259, 3323)	0.875
D-dimer (mg/L)	0.05	(–3.44, 0.89)	0.06	(–22.53, 37.58)	**0.003**
Fibrinogen (mg/dL)	29.60	(–216.00, 68.00)	54.01	(–83.00, 387.54)	0.409
ALT (U/L)	10	(–5, 98)	–0.5	(–26, 34)	0.147
AST (U/L)	4	(–17, 109)	0	(–35, 78)	0.959
Change from baseline on the 5th day of FVP					
Lymphocyte (10^6/L)	385	(–1390, 750)	95	(–450, 1170)	0.289
NLR	–0.31	(–9.11, 21.62)	–0.41	(–10.56, 13.69)	0.945
CRP (mg/dL)	–0.11	(–10.77, 46.13)	–0.23	(–8.30, 27.40)	0.920
LDH (U/L)	–6.5	(–304, 140)	14	(–606, 345)	0.255
Ferritin (µg/L)	28	(–637, 760)	196	(–269, 2973)	0.132
D-dimer (mg/L)	–0.04	(–3.07, 1.28)	0.10	(–24.17, 39.77)	0.883
Fibrinogen (mg/dL)	37	(–144, 415)	114	(–210, 370)	0.139
ALT (U/L)	16	(–5, 96)	5	(–11, 218)	0.872
AST (U/L)	6	(–45, 83)	5	(–12, 151)	0.437

* Mann–Whitney U test was used for statistical analysis.

with FVP treatment. TTD was 3.64 ± 4.60 and 5.94 ± 5.68 days in the low and high uric acid groups, respectively (p = 0.075).

This study has some limitations. First, it is a single-center study with a limited number of patients. Second, follow-up on the virological cure was not available. Follow-up was not available beyond the hospital stay, and only in-hospital events were recorded. Serum and intracellular FVP levels and HGPRT activity were not defined. Regardless, this study is the first to explore the possible association of baseline uric acid levels and the outcome of FVP treatment among COVID-19 patients. In this cohort of consecutive cases treated with FVP, excluding patients with underlying conditions/comedications that might affect serum uric acid levels, our results indicate that people with low baseline uric acid levels do not respond better to FVP treatment than the patients with higher uric acid levels.

Author contribution statement

Contributed to conception or design: ACİ, EK, OU, SU. Contributed to the acquisition, analysis, or interpretation: ACİ, EK, NCB, TKS, OAU. Drafted the manuscript: ACİ, EK. Critically revised the manuscript: OU, SU. Gave final approval: ACİ, EK, NCB, TKS, OAU, OU, SU.

Acknowledgement/Disclaimers/Conflict of interest

The authors would like to acknowledge the contributions of numerous physicians, nurses, and healthcare personnel of Hacettepe University's COVID-19 response team for their selfless efforts in follow-up and care of the patients. Authors declare that there is no conflict of interest.

Informed consent

Institutional review board approval was granted from the Hacettepe University Ethical Committee for Non-interventional Studies (GO 20/354).

References

1. Furuta Y, Takahashi K, Kuno-Maekawa M, Sangawa H, Uehara S et al. Mechanism of action of T-705 against influenza virus. Antimicrobial Agents and Chemotherapy 2005; 49 (3): 981-986. doi: 10.1128/AAC.49.3.981-986.2005
2. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antiviral Research 2018; 153: 85-94. doi: 10.1016/j.antiviral.2018.03.003
3. Wang M, Cao R, Zhang L, Yang X, Liu J et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research 2020; 30 (3): 269-271. doi: 10.1038/s41422-020-0282-0
4. Naesens L, Guddat LW, Keough DT, van Kuilenburg AB, Meijer J et al. Role of human hypoxanthine guanine phosphoribosyltransferase in activation of the antiviral agent T-705 (favipiravir). Molecular Pharmacology 2013; 84 (4): 615-629. doi: 10.1124/mol.113.087247